UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

TXR NO: 0054361

DATE: September 20, 2006

SUBJECT: BAS 800H: Early Mortality in the Mouse Cancer Study

PC Code: 118203; DP Barcode: 332665

FROM: Jessica Kidwell, Executive Secretary
Dose Adequacy Review Team
Health Effects Division (7509P)

THROUGH: Jess Rowland, Chair
Dose Adequacy Review Team
Health Effects Division (7509P)

TO: Joanne Miller, Product Manager
Tracy White, Reviewer
Herbicide Branch, Registration Division (7505P)

In response to BASF Toxicologist Jim Sherman's emails (attached) regarding early mortality in the mouse carcinogenicity study (using C57BL/6NCrl mice supplied by Charles River, Germany), the DART recommends that if 75% mortality is noted in any male group (control or treated), then an early sacrifice should be performed in all groups of male mice. The female mice should continue until scheduled termination unless a similar increase in mortality is seen.

This memo documents the USEPA DART's approval for termination of this study before 18 full months of treatment as described above.

Note to Registrant: Please reference this DART memo in the final study submission to EPA as justification for this action.

DART Members in Attendance at the September 19, 2006 Meeting: (Signature indicates concurrence with the report unless otherwise stated.)

William Burnam

Marion Copley

Jessica Kidwell

Jess Rowland

Yung Yang

ATTACHMENTS: EMAILS FROM JIM SHERMAN, BASF TO JESS ROWLAND, EPA ON 9/18/06 AND 9/19/06

----- Forwarded by Jess Rowland/DC/USEPA/US on 09/18/2006 03:37 PM -----

James H Sherman <james.sherman@basf.com>
09/18/2006 03:33 PM

To Jess Rowland/DC/USEPA/US@EPA
cc
Subject Re: Early Mortality in the Mouse Cancer Study with BAS 800 H

James H Sherman, Ph.D., DABT
Toxicologist Sr

Phone: 1-919-547-2930
E-mail: james.sherman@basf.com
Postal Address:

BASF - The Chemical Company

To rowland.jess@epa.
cc Charles E Hastings /NVA/RTP/BASF-CORP/BASF@

09/07/2006 10:53 AM BASF-CORP

Subject Early Mortality in the Mouse Cancer Study with BAS 800 H

Jess:

As discussed this morning, we are experiencing some early mortality in the mouse carcinogenicity study with BAS 800 H. The early mortality seems to be due to the specific mouse strain we are using, and is not a compound-specific effect, as we see the comparable results in other mouse studies that were initiated in the same time frame. In an effort to ensure the acceptability of our studies, we would appreciate some general guidance from the USEPA.

Pursuant to our meetings with the DART committee, we initiated dosing in the BAS 800 H mouse study on May 10, 2005. After approximately one year of treatment an increased incidence of unscheduled deaths began to be recorded in mice in control and all treatment groups. After 16 months of treatment, survival in all treatment groups is >50%. As such, the study has met the acceptance criteria for no less than 50% survival at 15 months. However, because the rate of unscheduled deaths is increasing, we have some concern that >25% survival may not be achieved in all treatment groups if the terminal sacrifice is carried out on November 8 and 9, as scheduled.

The specific questions we have are:

1) If 75% mortality is noted in any group (control or treated), should we perform an early sacrifice? At this point, we feel that would not happen until the mice had been treated for at least 17 months.

2) Since we do have an extra treatment group in this study (4 treated and a control group for each sex), is it better to examine survival of all control treatment groups rather than focusing on a single group? For

example, if only the survival in the second highest dose group in a single
sex drops below 25%, should we just continue the study?

3) If we terminate the study before the scheduled sacrifice at 18 months, is there a formal mechanism whereby we can gain USEPA approval for terminating the study before 18 full months of treatment?

In an effort to help in your assessment, I have included the most recent interval mortality report for the study.

Thank you for your continuing guidance as we proceed in our product development program.

Best regards,

Jim

(See attached file: 01177.pdf)

James H Sherman, Ph.D., DABT
Toxicologist Sr

Phone: -919-547-2930
E-mail: james.sherman@basf.com
Postal Address:

BASF - The Chemical Company

01177.pdf

BASF - DATATOX-F1 R14

Study: 87C0414/01177

INTERVAL MORTALITY REPORT

Print Date: 07-Sep-2006
Print Time: 10:02:41
Table : IA
Page : 1

Sex: Male

Group			0			1			2			3			4
No. of Animals			0 ppm 50			1 ppm 50			5 ppm 50			25 ppm 50			75 ppm 50
Period Ending (Day)	Sch	Unsch Prd	Unsch Tot	Avl	Sch	Unsch Prd	Unsch Tot	Avl	Sch	Unsch Prd	Unsch Tot	Avl	Sch	Unsch Prd	Unsch Tot	Avl
28				50				50				50				50
56				50				50				50				50
84		2%	2%	49				50		2%	2%	49				50
112				49				50				49				50
140				49		2%	2%	49				49				50
168				49				49				49				50
196				49				49				49				50
224		2%	4%	48				49				49				50
252				48		2%	4%	48				49				50
280				48				48				49				50
308				48				48				49		2%	2%	49
336				48				48				49				50
364				48		2%	6%	47		2%	4%	48				49
392		2%	6%	47		9%	14%	43		2%	6%	47		2%	4%	48
420		6%	12%	44		7%	20%	40		6%	12%	44		6%	10%	45
448		9%	20%	40		18%	28%	36		11%	22%	39		4%	14%	43
476		23%	38%	31		17%	40%	30		21%	38%	31		14%	26%	37
483		3%	40%	30		10%	46%	27				31		3%	28%	36
485		7%	44%	28		4%	48%	26		3%	40%	30				36

File: 01177.pdf

BASF - DATATOX-F1 R14

Study: B7C0414/01177

INTERVAL MORTALITY REPORT

Print Date: 07-Sep-2006
Print Time: 10:02:04
Table : 1A
Page : 1

Sex: Female

Group				0				2				3				4				5
No. of Animals				0 ppm 50				5 ppm 50				25 ppm 50				75 ppm 50				150 ppm 50
Period Ending (Day)	Sch	Unsch Prd	Unsch Tot	Avl	Sch	Unsch Prd	Unsch Tot	Avl	Sch	Unsch Prd	Unsch Tot	Avl	Sch	Unsch Prd	Unsch Tot	Avl	Sch	Unsch Prd	Unsch Tot	Avl
28				50				50				50				50				50
56				50				50				50				50				50
84				50				50				50				50				50
112				50				50				50				50				50
140				50				50				50				50				50
168				50				50				50				50				50
196				50				50		2%	2%	49				50				50
224				50				50				49		2%	2%	49				50
252				50				50				49				49				50
280				50				50		2%	4%	48				49				50
308		2%	2%	49				50				48				49				50
336				49				50				48				49				50
364				49		4%	4%	48				48				49				50
392		2%	4%	48		2%	6%	47				48		2%	4%	48				50
420		2%	6%	47		2%	8%	46		13%	16%	42		2%	6%	47		2%	2%	49
448		4%	10%	45		2%	10%	45		10%	24%	38		11%	16%	42		2%	4%	48
476		9%	18%	41		11%	20%	40		8%	30%	35		7%	22%	39		8%	12%	44
483		2%	20%	40		3%	22%	39		3%	32%	34		5%	26%	37		2%	14%	43
484		3%	22%	39				39				34				37				43

File: 01177.pdf

----- Forwarded by Jess Rowland/DC/USEPA/US on 09/19/2006 08:42 AM -----

James H Sherman <james.sherman@basf.com>	To	Jess Rowland/DC/USEPA/US@EPA
09/19/2006 08:18 AM	cc	
	Subject	Fw: BAS 800 H: mouse study; Mortality

Jess:

Below is the most recent mortality data from the mouse study with BAS 800
H.

Thanks for working with me on this.

Best regards,

Jim
James H Sherman, Ph.D., DABT
Toxicologist Sr

Phone: 1-919-547-2930
E-mail: james.sherman@basf.com
Postal Address:

BASF - The Chemical Company

----- Forwarded by James H Sherman/APD/RTP/BASF-CORP/BASF on 09/19/2006
08:15 AM -----

	Georgia Cunha/BASF-AG/BASF	
To	SF@EUROPE	James H Sherman/APD/RTP/BASF-CORP/BASF@B ASF-CORP
cc	09/19/2006 04:20 AM	Werner Mellert/ZH/BASF-AG/BASF@EUROPE
Subject		BAS 800 H: mouse study; Mortality

Information from 18/09:

males:	Gr.0/ 0	ppm	= 46%
	Gr.1/ 1	ppm	= 58%
	Gr.2/ 5	ppm	= 42%
	Gr.3/25	ppm	= 30%
	Gr.4/75	ppm	= 30%

females:	Gr.0/ 0	ppm	= 28%
	Gr.2/ 5	ppm	= 30%
	Gr.3/ 25	ppm	= 36%
	Gr.4/ 75	ppm	= 32%
	Gr.5/150	ppm	= 16%

Regards,

Georgia Cunha
Mechanistic Toxicology

Phone: +49 621 60-58160, E-Mail: georgia.cunha@basf.com
Postal Address: BASF Aktiengesellschaft, GV/TD - Z470, D-67056
Ludwigshafen, Germany

BASF - The Chemical Company

13544

R132691

Chemical:	Benzamide, 2-chloro-5-[3,6-dihydro-3-methyl-2,6-dioxo-4-(trifluoromethyl)-1(2H)-pyrimidinyl]-4-fluoro-N-[[methyl(1-methylethyl)amino]sulfonyl]-
PC Code:	118203
HED File Code:	13000 Tox Reviews
Memo Date:	9/20/2006
File ID:	TX0054361
Accession #:	412-07-0024

HED Records Reference Center
11/9/2006